REVIEW

The Long and Short of IT: intestinal failure-associated liver disease (IFALD) in adults—recommendations for early diagnosis and intestinal transplantation

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ABSTRACT

Intestinal failure-associated liver disease (IFALD) often presents in adults unexpectedly with advanced disease. Non-invasive tests can be falsely reassuring. Patients with 'ultrashort' intestine (<20 cm) ending in a stoma are at particular risk of developing IFALD, which may occur rapidly. Recent experience and studies suggest that IFALD can be reversed by isolated intestine transplant occurring before the development of high grade fibrosis or cirrhosis. Post-transplant survival is superior for isolated intestinal grafts compared with liver containing intestinal grafts; waiting time and waiting list mortality is higher for a combined graft, and donor liver supply is limited. Therefore, the aim of clinicians treating patients with intestinal failure should be to identify IFALD early and refer to an intestinal transplant centre while isolated intestine transplantation can be contemplated and before the liver disease has progressed to a stage requiring consideration of combined liver and intestinal transplantation.

INTRODUCTION

The primary function of the gastrointestinal tract is the digestion and assimilation of fluids, electrolytes and nutrients. Intestinal failure (IF) is therefore said to occur when their absorption is insufficient to maintain health. It may result from extensive mucosal damage, dysmotility or surgical resection and can be temporary (for instance, in postoperative ileus), remediable (for instance by surgical reconstruction) or permanent (for instance, short bowel syndrome).¹ By definition, IF requires the absorptive deficit to be supplemented intravenously, and parenteral nutrition (PN) support for

IF can be continued indefinitely as long as venous access is maintained. The majority of deaths occurring while receiving long-term PN are due to the underlying disease that caused the IF itself.^{2–4} A significant exception to this is the development of life-threatening liver disease, which may be responsible for between 3%⁵ and 26%⁶ of all deaths on PN. IF-associated liver disease (IFALD) has been reported to be responsible for 3.6%³ and 9%⁴ of all-cause mortality from the two largest UK adult national centres in St Marks and Salford, respectively.

The intestinal failure-associated liver disease

The aetiology of IFALD is likely to be multifactorial as is reflected in the different histological patterns of liver damage that usually overlap.⁷ Profound cholestasis can be associated with the use of soy-based lipid emulsions due to phytosterol inhibition of the farnesoid X receptor but equally through lack of physiological stimulation of cholestasis and the loss of FGF signalling through interruption of enterohepatic cycling.⁸ Cholestasis may be exacerbated by the use of drugs and as a result of infection. Prolonged cholestasis may result in biliary epithelial damage known as 'cholate' stasis resulting in metallothionein protein deposition in periportal areas and ultimately the loss of biliary epithelium. This further reduces biliary excretion and leads to periportal fibrosis. Significant fat deposition (steatosis) may occur as a result of the non-physiological delivery of lipid micelles in PN or as a result of de novo lipogenesis within the liver due to excess carbohydrate

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delivery and the lack of incretin stimulation of enteropancreatic endocrine secretion. Endoplasmic reticulum stress and the activation of the unfolded protein response by long-chain fatty acids may also stimulate lipogenesis.⁹ The subsequent generation of reactive oxygen species can result in hepatocyte damage and inflammation leading to pericellular fibrosis. Progressive fibrosis resulting in cirrhosis and end-stage liver disease can occur rapidly, within a year in both children¹⁰ and adults.¹¹

Given the heterogeneity of the pathological lesion in IFALD, a unifying definition is elusive. Some have attempted to define it on the basis of persistently abnormal blood tests, greater than 150% of the upper limit of normal,¹² others by the presence of particular appearances on liver biopsy. Neither precludes the potential for pre-existing or superadded pathology to contribute¹³ on which the additive effect of IF or PN use is uncertain. The prevalence of IFALD is therefore difficult to quantify and has been variously estimated at 15%–40%.¹¹ Further clarity is unlikely to be forthcoming given the current European Society for Parenteral and Enteral Nutrition (ESPEN) definition of IFALD as *'the presence of abnormal liver function tests and/or evidence of radiological and/or histological liver abnormalities in the absence of another primary parenchymal liver pathology'* and furthermore states that abnormal liver histology is not mandatory for diagnosis.¹⁴

The expression of IFALD differs between adults and children, the latter being relatively more susceptible to severe cholestasis than steatosis. It may behave differently in neonates due to delayed maturation of liver enzyme pathways and the greater potential for intestinal adaptation with growth but in older children IFALD is more likely to mimic the adult situation.¹⁵

Certain factors associated with a higher risk of development of IFALD have been identified from retrospective series. Not surprisingly the risk appears inversely proportionate to the length of remaining intestine, although whether this relates to the amount of PN required or physiological factors relating to intestinal function is unclear.^{4 16–21} The presence of a colon in continuity appears protective,¹⁶ which could be due to the additional absorptive capacity resulting or microbial products in the portal circulation. A high intake of soy-based lipid emulsion (>1 g/kg/day) was found to be associated with a higher risk of IFALD.¹³

Since the introduction of new intravenous lipid sources and a greater awareness of modifiable risk factors, the prevalence of severe IFALD appears to have been dropping.²² This is particularly prominent in the paediatric population, although there is a suggestion that underlying fibrosis may continue despite reversal of overt cholestasis and improvement of liver blood tests.^{23 24} This would suggest that IFALD in this group may be delayed rather than prevented.

The diagnosis of IFALD

Identifying the onset of IFALD can be challenging as the ideal non-invasive test has not yet been found. Liver blood tests abnormalities are common in parenterally fed patients. A persistent rise in alkaline phosphatase has previously been labelled as 'cholestatic' but equally appears to correlate with the degree of steatosis in this population.²⁵ However, blood tests can remain remarkably static or even within normal range until end-stage disease supervenes unexpectedly, often marked only by a rapid elevation of serum bilirubin (figure 1). One reason for the late presentation of end-stage IFALD is that with reduced portal inflow to the liver (as seen in short bowel syndrome), the usual portal hypertensive triad of oesophageal varices, encephalopathy and ascites does not occur. Insidious fatigue or weight loss may be the only clinical sign of severe IFALD.

There have been numerous attempts to monitor liver disease without recourse to biopsy including the use of ultrasound elastography ('Fibroscan')^{26 27} and MRI spectroscopy.^{25 28} These have shown limited ability to identify progressive liver disease in this setting and cannot yet be relied on. At the current time, liver biopsy remains the best modality for identifying and monitoring the progression of the condition, despite its obvious limitations. In our experience, clinicians are often surprised by the advanced degree of liver disease found after doing a biopsy their patients who appear well and have reassuring fibroscan results and liver blood tests.

The management of IFALD

The primary consideration in managing IFALD is to prevent, where possible, its onset and progression. In view of what we know of the associated aetiological factors, current professional bodies recommend the use of non-soy-based emulsions, and limitation of average lipid delivery to <1 g/kg/day where possible,¹⁴ but at least 1 g/kg per week to avoid essential fatty acid deficiency. In addition, the rate of carbohydrate delivery should not exceed estimated baseline oxidation limits, and micronutrient balance including key antioxidants (for instance, selenium) should be maintained. Vitamin D levels should be measured and supplemented. Patients should be encouraged to eat to stimulate enteroendocrine secretions even if absorption is minimal. Cyclical delivery of PN is thought to be advantageous, although definitive evidence is limited. Restoration of intestinal continuity should be sought where possible, particularly if there is residual colon out of circuit.

Suspicion of developing IFALD should prompt liver biopsy in the first instance. Severe cholestasis in adults is unusual but can be managed by significant reduction of lipid delivery and careful measurement of trace elements that undergo biliary excretion such as

Figure 1 Sequential liver blood tests of two patients with IFALD referred to Cambridge for intestinal transplantation. The lack of utility in diagnosing advanced IFALD is demonstrated as well as the potential for rapid deterioration thereafter. Straight lines represent the upper limit of normal for each respective test. (A) A 20-year-old patient underwent total enterectomy and pancreatotomy for an abdominal desmoid tumour associated with familial adenomatous polyposis coli having undergone prior pan proctocolectomy. The pylorus was closed at the time of surgery, and the bile duct was drained into the stomach, which was in turn drained by a 24F venting gastrostomy. Total parenteral nutrition was instituted with insulin added to the bag. At presentation 2 years later with fatigue and weight loss, there were no other clinical features of portal hypertension, and liver blood tests were normal. Liver biopsy demonstrated established cirrhosis. The chart shows representative monthly blood tests up until the time of transfer onto a palliative care pathway. The block arrow shows the time at which liver biopsy was carried out. Note the rapid deterioration of liver blood tests (especially bilirubin) and the short period of time before clinical deterioration precluded transplantation. (B) A 30-year-old patient with a long history of multiple laparotomies and resections for small intestinal Crohn's disease was left with 50 cm of small intestine to a stoma and started on Home Parenteral Nutrition (HPN). Three years later, a liver biopsy was reported as showing established cirrhosis. At the time of biopsy, the alkaline phosphatase was markedly elevated, but the bilirubin and alanine aminotransferase (ALT) were within normal range. Two years later, the patient received a multivisceral transplant (block arrow). The chart shows representative monthly liver blood tests for the 5 months prior to transplant and 2 months after transplant.

Manganese, which can accumulate in the basal ganglia and cause extrapyramidal motor disorders.

Established IFALD mandates *consideration* of transplantation. A 5-year follow-up study of European patients who met established criteria for intestine containing transplants showed only two categories where outcomes were poor without transplantation.²⁹ These were patients with IFALD or those with desmoid tumours threatening the mesenteric circulation. IFALD

Figure 2 Data reproduced from the US 2016 Annual Data Report of Scientific Registry of Transplant Recipients.³¹ (A) Patient survival among adult deceased donor intestine transplant recipients, 2009–2011, by age and transplant type. Patient survival estimated using unadjusted Kaplan-Meier methods. For recipients of more than one transplant during the period, only the first is considered. This demonstrates the lower survival rates for adults receiving a liver-containing intestinal graft (IN-LI) compared with IN-LI recipients under the age of 18 years or those of all ages receiving intestine grafts alone (IN). (B) Pretransplant mortality rates among candidates waitlisted for intestine transplant by liver colisting. Mortality rates are computed as the number of deaths per 100 patient-years of awaiting in the given year. Individual listings are counted separately. Intestine–liver colisting is computed in a time-dependent manner. Rates with less than 10 patient-years of exposure are not shown. This demonstrates the higher waiting list mortality for adults listed for liver and intestine (IN-LI) grafts compared with those under the age of 18 years and those of all ages listed for intestine grafts alone (IN).

was at one time the major indication for paediatric intestinal transplantation, the majority of which required a liver graft in addition to the intestine due to the late stage of presentation. Established IFALD in adults may progress rapidly as a result of late diagnosis and carries a poor prognosis.³⁰

IFALD and transplantation

Two recent developments have significantly changed practice in the transplantation management of IFALD. The first is the realisation that the outcome for full multivisceral grafts in adults is worse than for isolated intestinal transplantation or for the ‘modified multivisceral’ graft that does not include liver (figure 2A³¹). The reasons for this are not entirely clear. In addition, the waiting list mortality for patients listed for liver containing intestinal grafts is much higher than for other organ transplants (figure 2B^{31 32}). This may reflect the often advanced stage of liver disease present in the setting of IFALD that is not reflected by standard United Kingdom Model for End Stage Liver Disease (UKELD) scoring, but also the longer

Figure 3 Kaplan-Meier survival curves (uncensored) for transplantation with IFALD as the primary indication in Cambridge UK (2008–2018) separated by liver containing ($n=13$) or non-liver containing ($n=8$) grafts. In addition seven patients died of severe liver disease during this time period due to late referral. This demonstrates first the possibility of long-term survival without the need for liver transplantation despite moderately severe fibrosis due to IFALD, and second, the better outcomes for patients receiving intestinal grafts without liver. IFALD, intestinal failure-associated liver disease.

waiting times for patients requiring a combined transplant rather than intestine alone. The second is that it is becoming apparent that transplant of intestine alone, even in the presence of established IFALD, is compatible with good survival and improvement of the liver fibrosis (figures 3³³). However, once the liver disease has progressed too far, a liver containing graft is required. In some children, it has been possible to transplant liver alone given greater potential prospects for reversal of the intestinal failure; however, this is rarely an option for adults. Sequential transplant of liver then intestine may be feasible in adults, but it is not known how long the liver graft would tolerate the interval while on PN, and the possibility of anti-human Leucocyte antigen (HLA) antibody sensitisation might then preclude intestinal transplantation. In addition, pre-emptive intestinal transplantation to reverse liver fibrosis importantly allows for reallocation of the liver in this time of significant organ donor shortage. Clearly, therefore, it is important to identify patients with IFALD at an early stage, and this will require changes in current practice as the majority of patients referred for transplantation in this setting are already at an advanced stage.

Is it possible to identify patients who are likely to progress to IFALD?

The association of IFALD with intestinal length in most series is striking, particularly those that have identified patients with ‘ultrashort’ intestine as a separate group. There are varied definitions of ‘ultrashort’, and the anatomy can vary—most consider <10 cm

intestine beyond the duodeno-jejunal flexure in children and <20 cm in adults to be ‘ultrashort’. In some patients, there is insufficient intestinal length to form a stoma, and the duodenum may be oversewn and the stomach vented by gastrostomy. It is not uncommon for the duodenal suture line to break down and for a fistula to then form to the skin surface. This can be exceptionally difficult to manage due to the corrosive nature of the gastropancreaticoduodenal secretions. Other patients with an ultrashort bowel may have sufficient length to form a stoma, or to anastomose to a colonic remnant, then usually brought out as a colostomy. In some cases, the stomach has been anastomosed directly to transverse colon in this way. Patients with ‘ultrashort’ bowel are at very high risk of IFALD, but the risk varies according to the anatomy. Those in whom a very short length of jejunum is anastomosed to colon can experience long-term survival without liver disease, whereas this is extremely unlikely in those with an oversewn duodenum who generally develop advanced liver disease within 2–3 years.

Appropriate management of the patient with ‘ultrashort bowel’ therefore requires cognisance of the fact that early development of IFALD is common in this setting in adults and that transplantation is required before the development of significant liver disease, thereby allowing the opportunity for intestine-only grafts. Given the limitations of non-invasive liver tests and the potential for rapid progression after development of hyperbilirubinaemia, a proactive approach is appropriate. We would therefore recommend discussion with an intestinal transplant centre after significant enterectomy in order not to avoid the potential transplantation window and to plan a suitable monitoring strategy with baseline liver biopsy if necessary.

How do we assess the suitability of patients with IFALD for isolated intestinal transplantation?

There are no clearly identified criteria for the assessment of the degree of liver damage that is compatible with recovery after isolated intestinal transplantation. However it is clear that even established liver fibrosis can resolve following transplantation and emancipation from PN.³² Patients with established cirrhosis on liver biopsy are unsuitable, as are many of those with ‘severe’ fibrosis or who are ‘precirrhotic’. At present, therefore, each case needs to be treated individually until it is possible to establish clear criteria on which to base the decision. Currently, this is predominantly based on biopsy appearances and the presence or absence of portal hypertension; however, there may be other considerations or tests that could stratify the degree of damage and assist in decision making. In cases of severe fibrosis where there may be uncertainty, a liver containing donor block may be needed with reallocation of the liver if found not to be required during the operation. Ideally, portal drainage would be achieved in isolated intestinal grafts to prevent the

possibility of encephalopathy occurring with systemically drained intestine, particularly after restoration of colonic continuity.

Summary and recommendations for adults

1. A baseline liver biopsy and cholecystectomy should ideally be undertaken if feasible at the time of extensive enterectomy.
2. Liver-sparing intestinal transplantation should be considered proactively rather than awaiting the development of significant liver disease.
3. Non-invasive measurements of liver function are currently inadequate to exclude IFALD, and the development of significant liver blood test abnormalities may only occur in advanced liver disease. Clinical and radiological features of portal hypertension may develop late in the course of IFALD associated with short bowel. Liver biopsy is currently the only reliable indicator of the impending need for intestinal transplantation and should therefore be performed early enough after commencing HPN in patients with short bowel syndrome to identify the development of IFALD. The timing of initial liver biopsy and subsequent surveillance biopsies will depend on the patient's clinical state, ultimate suitability for transplantation, intestinal anatomy and the rate of progression of changes.
4. Due to the potential for rapid development and progression of IFALD patients should be discussed with an intestinal transplant centre at the earliest possible opportunity following enterectomy that leaves them with an ultrashort bowel (<20 cm small intestine), unless they are clearly not suitable for consideration of transplantation due to comorbid factors.
5. Further research is required in the following areas:
 - a. The performance of non-invasive tests against liver biopsy in identifying IFALD at early enough stages to plan liver-sparing intestinal transplantation.
 - b. The time course of development of IFALD for patients with different anatomical configurations postenterectomy in the modern era.
 - c. The optimal timing of initial and follow-up liver biopsies in patients with short bowel syndrome on HPN.
 - d. The effect of IF and long-term PN on pre-existing liver disease including the effects on transplanted liver.
 - e. Criteria by which to select patients with IFALD who can receive isolated intestinal grafts rather than combined liver and intestinal transplantation.

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